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**UNITED STATES DISTRICT COURT  
DISTRICT OF NEVADA**

AMARIN PHARMA, INC. and AMARIN  
PHARMACEUTICALS IRELAND LIMITED,

Plaintiffs,

v.

HIKMA PHARMACEUTICALS USA INC.,  
*et al.*,

Defendants.

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CASE NO.: 2:16-cv-02525-MMD-NJK

(Consolidated with  
2:16-cv-02562-MMD-NJK)

**PLAINTIFFS' POST-TRIAL BRIEF**

**TABLE OF CONTENTS**

I.	INTRODUCTION .....	1
II.	DEFENDANTS INDUCE INFRINGEMENT OF ALL ASSERTED CLAIMS .....	4
A.	Defendants Intend to Induce Clinicians to Prescribe Their Respective ANDA Products for at Least 12 Weeks .....	5
B.	Defendants Intend to Induce Clinicians to Prescribe Their Respective ANDA Products to Achieve The Claimed Lipid Effects .....	8
C.	Defendants Intend to Induce Administration “Without Concurrent Lipid Altering Therapy” .....	13
III.	DEFENDANTS HAVE NOT MET THEIR BURDEN OF PROVING THAT THE ASSERTED CLAIMS WERE OBVIOUS .....	14
A.	Defendants Have Not Shown That a POSA Would Have Reasonably Expected Success With an EPA Formulation.....	14
B.	Defendants Have Not Shown That a POSA Would Have Been Motivated to Arrive at the Claimed Invention.....	21
C.	Defendants Have Not Proven That It Would Have Been “Obvious to Try” the Claimed Invention.....	23
D.	Objective Indicia Reinforce the Non-Obviousness of the Asserted Claims .....	25
IV.	DEFENDANTS WAIVED THEIR WRITTEN DESCRIPTION DEFENSE.....	30

**TABLE OF AUTHORITIES**

<b>Cases</b>	<b>Page(s)</b>
<i>Alcon Research, Ltd. v. Apotex Inc.</i> , 687 F.3d 1362 (Fed. Cir. 2012).....	16
<i>AstraZeneca v. Apotex Inc.</i> , 633 F.3d 1042 (Fed. Cir. 2010).....	5, 6
<i>Bayer Schering Pharma AG v. Barr Labs., Inc.</i> , 575 F.3d 1341 (Fed. Cir. 2009).....	24
<i>Bayer Schering Pharma AG v. Lupin Ltd.</i> , 676 F.3d 1316 (Fed. Cir. 2012).....	9, 11, 12
<i>In re Copaxone Consolidated Cases</i> , No. CV 14-1171-GMS, 2017 WL 401943 (D. Del. Jan. 30, 2017).....	16
<i>Eli Lilly &amp; Co. v. Teva Parenteral Meds. Inc.</i> , 845 F.3d 1357 (Fed. Cir. 2017).....	4, 29
<i>Grunenthal GMBH v. Alkem Labs. Ltd.</i> , 919 F.3d 1333 (Fed. Cir. 2019).....	4, 7, 8
<i>Hoffmann-La Roche Inc. v. Apotex Inc.</i> , 748 F.3d 1326 (Fed. Cir. 2014).....	16
<i>HZNP Medicines LLC v. Actavis Laboratories UT, Inc.</i> , 940 F.3d 680 (Fed. Cir. 2019).....	7
<i>Knoll Pharm. Co. v. Teva Pharm. USA, Inc.</i> , 367 F.3d 1381 (Fed. Cir. 2004).....	29
<i>KSR Int’l Co. v. Teleflex Inc.</i> , 550 U.S. 398, (2007).....	25
<i>Leo Pharm. Prods., Ltd. v. Rea</i> , 726 F.3d 1346 (Fed. Cir. 2013).....	24
<i>Merck &amp; Co. v. Teva Pharmaceuticals USA</i> , 395 F.3d 1364 (Fed. Cir. 2005).....	16
<i>Otsuka Pharm. Co. v. Torrent Pharm. Ltd., Inc.</i> , 99 F. Supp. 3d 461 (D.N.J. 2015).....	8

1	<i>Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.</i> ,	
2	323 F. Supp. 3d 566, 587 (D. Del. 2018) <i>aff'd sub nom. Persion Pharm. LLC</i>	
3	<i>v. Alvogen Malta Operations Ltd.</i> , 945 F.3d 1184 (Fed. Cir. 2019).....	8, 9
4	<i>Polaris Indus., Inc. v. Arctic Cat, Inc.</i> ,	
5	882 F.3d 1056 (Fed. Cir. 2018).....	21
6	<i>Sanofi–Aventis Deutschland GmbH v. Glenmark Pharm. Inc., U.S.A.</i> ,	
7	748 F.3d 1354 (Fed. Cir. 2014).....	17, 20, 25
8	<i>Sanofi v. Glenmark Pharm. Inc., USA</i> ,	
9	204 F. Supp. 3d 665, 684 (D. Del. 2016), <i>aff'd sub nom. Sanofi v. Watson</i>	
10	<i>Labs. Inc.</i> , 875 F.3d 636 (Fed. Cir. 2017).....	7, 13
11	<i>Sanofi v. Watson Labs. Inc.</i> ,	
12	875 F.3d 636 (Fed. Cir. 2017).....	5, 10, 13
13	<i>Takeda Pharmaceuticals U.S.A., Inc. v. West-Ward Pharmaceutical Corp.</i> ,	
14	785 F.3d 625 (Fed. Cir. 2015).....	7, 8
15	<i>United Therapeutics Corp. v. Sandoz Inc.</i> ,	
16	No. 12-CV-01617, 2014 WL 4259153 (D.N.J. Aug. 29, 2014) .....	8
17	<i>Vanda Pharm. Inc. v. West-Ward Pharm. Int'l Ltd.</i> ,	
18	887 F.3d 1117 (Fed. Cir. 2018).....	4, 5
19	<i>WBIP, LLC v. Kohler Co.</i> ,	
20	829 F.3d 1317 (Fed. Cir. 2016).....	27
21	<b>Statutes</b>	
22	35 U.S.C. § 103.....	20
23	35 U.S.C. § 282(c) .....	21

## TABLE OF ABBREVIATIONS

<b>Asserted Patents</b>	U.S. Patent No. 8,293,728 ('728 Patent) (PX 21); U.S. Patent No. 8,318,715 ('715 Patent) (PX 22); U.S. Patent No. 8,357,677 ('677 Patent) (PX 25); U.S. Patent No. 8,367,652 ('652 Patent) (PX 26); U.S. Patent No. 8,431,560 ('560 Patent) (PX 30); U.S. Patent No. 8,518,929 ('929 Patent) (PX 31)
<b>Asserted Claims</b>	Claims 1 and 16 of the '728 Patent; Claim 14 of the '715 Patent; Claims 1 and 8 of the '677 Patent; Claim 1 of the '652 Patent; Claims 4 and 17 of the '560 Patent; and Claims 1 and 4 of the '929 Patent
<b>Amarin</b>	Plaintiffs Amarin Pharma, Inc. and Amarin Pharmaceuticals Ireland Limited
<b>ANDA</b>	Abbreviated New Drug Application
<b>apo B</b>	apolipoprotein B
<b>ATP-III</b>	American Heart Association, <i>Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report</i> , 106 Circulation 3143 (2002) (PX 989/DX 1876) [Stipulated Prior Art (ECF No. 324 ¶ 64)]
<b>Bays 2008</b>	Bays et al., <i>Prescription Omega-3 Fatty Acids and Their Lipid Effects: Physiologic Mechanisms of Action and Clinical Implications</i> , 6 Expert Rev. Cardiovasc. Ther. 391 (2008) (PX 486) [Stipulated Prior Art (ECF No. 324 ¶ 69)]
<b>Castaldo</b>	Castaldo, <i>Switching statin-treated patients from fenofibrate to the prescription omega-3 therapy icosapent ethyl: a retrospective case series</i> , 32 Drugs & Therapy Perspective 162 (2016) (PX 866)
<b>Defendants</b>	Defendants Hikma Pharmaceuticals USA, Inc., Hikma Pharmaceuticals International Limited, Dr. Reddy's Laboratories, Inc., and Dr. Reddy's Laboratories, Ltd.
<b>Defendants' Labels</b>	Hikma 2019 Proposed Label (PX 1203); DRL 2020 Proposed Label (PX 1209)
<b>DHA</b>	ethyl docosahexaenoic acid

<b>DPF</b>	Defendants' Post-Trial Proposed Findings of Fact and Conclusions of Law (ECF No. 373)
<b>EPA</b>	ethyl eicosapentaenoic acid or icosapent ethyl
<b>FDA</b>	U.S. Food and Drug Administration
<b>Fialkow</b>	Fialkow, <i>Omega-3 Fatty Acid Formulations in Cardiovascular Disease: Dietary Supplements Are Not Substitutes for Prescription Products</i> , 16 AM. J. Cardiovascular Drugs 229 (2016) (PX 852)
<b>g</b>	gram(s)
<b>Grimsgaard</b>	Grimsgaard et al., <i>Highly Purified Eicosapentaenoic Acid and Docosahexaenoic Acid in Humans Have Similar Triacylglycerol-Lowering Effects but Divergent Effects on Serum Fatty Acids</i> , 66 AM. J. CLIN. NUTR. 649 (1997) (DX 1530) [Stipulated Prior Art (ECF No. 324 ¶ 41)]
<b>Hayashi</b>	Hayashi et al., <i>Decreases in Plasma Lipid Content and Thrombotic Activity by Ethyl Icosapentate Purified from Fish Oils</i> , 56(1) CURR. THERAP. RES. 24 (1995) (DX 1532) [Stipulated Prior Art (ECF No. 324 ¶ 39)]
<b>HDL-C</b>	high-density lipoprotein cholesterol
<b>IDL</b>	intermediate-density lipoprotein
<b>JELIS</b>	Japan EPA Lipid Intervention Study
<b>Karalis</b>	Karalis et al., <i>A Review of Clinical Practice Guidelines for the Management of Hypertriglyceridemia: A Focus on High Dose Omega-3 Fatty Acids</i> , 34 Adv Ther 300, 309 (PX 288)
<b>Kurabayashi</b>	Kurabayashi et al., <i>Eicosapentaenoic Acid Effect on Hyperlipidemia in Menopausal Japanese Women</i> , OBSTET. GYNECOL. 96:521 (2000) (DX 1534) [Stipulated Prior Art (ECF No. 324 ¶ 45)]
<b>LDL-C</b>	low-density lipoprotein cholesterol
<b>Lipitor label</b>	Lipitor Label 2007 (DX 3007)

<b>Lovaza Statistical Review</b>	Center for Drug Evaluation and Research, FDA, Application Number 21-654, Statistical Review(s) (2004) (Lovaza Statistical Review) (PX 939) [Stipulated Prior Art (ECF No. 324 ¶ 87)]
<b>MARINE</b>	Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12-Week Study with an Open-Label Extension to Evaluate the Efficacy and Safety of AMR101 in Patients with Fasting Triglyceride Levels $\geq 500$ mg/dL and $\leq 2000$ mg/dL (PX 807)
<b>Medical Review</b>	Center for Drug Evaluation & Research, FDA, <i>Medical Review(s)</i> , NDA No. 202057 (July 25, 2012) (PX 289)
<b>mg/dL</b>	milligram(s) per deciliter
<b>Mori 2000</b>	Mori et al., <i>Purified Eicosapentaenoic and Docosahexaenoic Acids Have Differential Effects on Serum Lipids and Lipoproteins, LDL Particle Size, Glucose, and Insulin in Mildly Hyperlipidemic Men</i> , 71 AM. J. CLINICAL NUTRITION 1085 (2000) (DX 1538) [Stipulated Prior Art (ECF No. 324 ¶ 46)]
<b>MSJ Opinion</b>	Court's Order on Motion for Summary Judgment (ECF No. 278)
<b>Nozaki</b>	Nozaki et al., <i>Effects of Purified Eicosapentaenoic Acid Ethyl Ester on Plasma Lipoproteins in Primary Hypercholesterolemia</i> , 62 INT'L J. VITAMIN & NUTRITION RES. 256-60 (1992) (DX 1541) [Stipulated Prior Art (ECF No. 324 ¶ 38)]
<b>POSA</b>	person of ordinary skill in the art
<b>PPF</b>	Plaintiffs' Post-Trial Proposed Findings of Fact and Conclusions of Law (ECF No. 374 [Original]/ECF No. 377 [Corrected])
<b>PX</b>	Plaintiffs' Exhibit

1	<b>REDUCE-IT</b>	Multi-Center, Prospective, Randomized, Double-Blind,
2		Placebo-Controlled, Parallel-Group Study to Evaluate the
3		Effect of AMR101 on Cardiovascular Health and Mortality in
4		Hypertriglyceridemic Patients with Cardiovascular Disease or
5		at High Risk for Cardiovascular Disease: Reduction of
6		Cardiovascular Events with EPA–Intervention Trial (PX 1189,
7		PX 271)
8	<b>TG</b>	triglyceride
9	<b>Trial Tr.</b>	Trial Transcript
10	<b>VASCEPA Label</b>	VASCEPA Label 2019 (PX 1186)
11	<b>von Shacky</b>	von Schacky, <i>A review of omega-3 ethyl esters for</i>
12		<i>cardiovascular prevention and treatment of increased blood</i>
13		<i>triglyceride levels</i> , Vascular Health and Risk Management
14		2(3):251 (2006) (DX 1605) [Stipulated Prior Art (ECF No. 324
15		¶ 82)]

## I. INTRODUCTION

The trial record confirms the contemporaneous observation of Dr. Steven Nissen of the Cleveland Clinic that “there’s still room for small companies to do innovative things” in the medical field. PPF ¶ 79. The testimony of both sides’ experts confirms that Vascepa®, the embodiment of the patented methods, was the first approved treatment for severe hypertriglyceridemia that reduces triglycerides (TGs) without increasing LDL-C. *Id.* ¶ 39. Thus, Amarin scientists for the first time demonstrated a way to reduce the risk of pancreatitis in patients with severe hypertriglyceridemia without exacerbating cardiovascular disease—again in Dr. Nissen’s words, “a real advance in the treatment of elevated triglycerides . . . all the benefit without the downside.” *Id.* ¶ 79. And the proven benefits of treating the severely hypertriglyceridemic (and others) with VASCEPA has dramatically expanded since then, as VASCEPA has now been shown (and is FDA-approved) to dramatically reduce cardiovascular risk in those patients—the first and only TG-lowering agent to demonstrate such a benefit.

Defendants seek to sell generic copies of VASCEPA prior to the expiration of Amarin’s Asserted Patents, which cover methods of treating severe hypertriglyceridemia with purified EPA. At trial, Defendants contended that they should be entitled to launch their generic products because, they assert, either they will not induce prescribers to infringe the Asserted Claims or those claims are invalid as obvious. The record refutes both assertions.

*Infringement.* Because their products meet all the compositional requirements of the claims, Defendants dispute induced infringement only with respect to a few categories of claim limitations: whether their labeling will encourage clinicians (1) to administer their products for at least 12 weeks, so as (2) to bring about certain effects on TG, LDL-C, and apo B, (3) in patients not receiving other concurrent lipid-altering therapy, such as statins.

With respect to the 12-week limitations, the labeling encourages clinicians to use Defendants’ products long term. Both sides’ experts agree that clinicians understand that the products are indicated to get TGs under 500 mg/dL *and keep them there*—an objective that will require, in the vast majority of cases, long-term administration of the drug, because the drug lowers

1 TGs but does not remedy the underlying causes of the very high TG levels. Moreover, the labeling  
2 further instructs clinicians, *prior to initiation of therapy*, to assess whether a patient's TG levels  
3 can be reduced through other means—for example, by adjusting their diet and exercise—thereby  
4 encouraging use of the drug in those whose condition is chronic or who otherwise need long-term  
5 therapy. The rest of the labeling reinforces the conclusion that clinicians will inevitably prescribe  
6 the drug for at least 12 weeks to many of their patients. That some prescribers may ignore the  
7 labeling to administer the drug to people with rapidly reversible, acute forms of severe  
8 hypertriglyceridemia is irrelevant. Nor has the clinical benefit, if any, of such acute use been  
9 clinically studied or FDA-reviewed.

10 The labeling will also encourage clinicians to administer EPA to reduce TGs and achieve  
11 the additional claimed lipid effects, which were established during the MARINE trial and  
12 expressly set forth in the labeling. The evidence shows that FDA includes these lipid effects in the  
13 labeling to reflect their clinical importance and facilitate the safe and effective use of the drug; that  
14 clinicians prescribe EPA intending and expecting those effects to occur; and that these effects will  
15 occur in a majority of patients. That some patients may respond differently is irrelevant, as  
16 inducement requires only that some clinicians will follow the labeling and prescribe in an  
17 infringing manner. Nor is it relevant that the lipid effects are not expressly recited in the indication  
18 itself. The labeling as a whole makes clear that the drug is safe and effective to reduce TGs in the  
19 severely hypertriglyceridemic while achieving the claimed lipid effects.

20 Finally, with respect to the claims requiring administration without concurrent lipid-  
21 altering therapy, the drug is approved as monotherapy and the indication itself calls for that use  
22 (as an adjunct to diet). If co-administration of another medication were required to achieve the  
23 indicated therapeutic benefit, the indication would reflect that. That the drug is also safe and  
24 effective when administered to patients receiving a statin does not change this. Because the  
25 labeling makes clear that EPA can be used *with or without* concurrent therapy, it encourages  
26 physicians to administer EPA as monotherapy in those patients who do not otherwise require statin  
27 therapy and as combination therapy in those who do. Defendants' conclusion—that the labeling  
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1 encourages *neither* monotherapy *nor* co-administration—defies common sense. It encourages  
2 *both*, depending upon physician judgment about patient needs. Indisputably, the labeling will  
3 encourage administration as monotherapy in those patients for whom a statin is not indicated.

4 *Obviousness.* Defendants did not prove by clear and convincing evidence that the POSA  
5 would have been motivated to use substantially pure EPA as a treatment for severe  
6 hypertriglyceridemia, or that such a person would have reasonably expected to avoid a substantial  
7 increase in LDL-C using EPA in those patients. The prior art taught that every drug approved for  
8 lowering TGs in the severely hypertriglyceridemic—whether niacin, fibrates, or omega-3-fatty  
9 acids—raised LDL-C dramatically in that population, even though they did not have that effect  
10 when administered to patients with lower TG levels. The POSA attributed this increase in LDL-C  
11 to the way TG-lowering drugs were understood to work in the severely hypertriglyceridemic—  
12 enhancing clearance of the superabundance of VLDL particles to LDL. The POSA expected EPA  
13 to work the same way. The prior art confirms that this mechanism of action was well established  
14 as (1) causing the LDL-C increases; and (2) applicable to omega-3-fatty acids, including EPA.

15 Additionally, the prior art, including one of the principal references that Defendants relied  
16 upon (Mori 2000), taught that one of the primary omega-3-fatty acids in Lovaza—DHA—  
17 conferred cardiovascular benefits that EPA (also in Lovaza) did not share. The POSA therefore  
18 would have had no reason to strip DHA from Lovaza, especially when such a person still would  
19 have expected the resulting EPA-only formulation to raise LDL-C. Defendants' reliance on some  
20 art reporting that EPA did not substantially raise LDL-C when given to patients with much lower  
21 TG levels does not save them. Defendants' art is not representative of the prior art as a whole. That  
22 art did not study EPA in the severely hypertriglyceridemic (a population in which clinical effects  
23 were known to be different). That art would not have altered the expectation—founded on long  
24 experience with a variety of TG-lowering drugs—that EPA would dramatically increase LDL-C  
25 in patients with severe hypertriglyceridemia.

26 Defendants also failed to rebut the strong showing of objective indicia of non-obviousness.  
27 These objective indicia include that, in the severely hypertriglyceridemic patient population,  
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VASCEPA unexpectedly (1) did not raise LDL-C, (2) lowered apo B, and (3) reduced cardiovascular risk; that clinicians were skeptical of, and surprised by, VASCEPA's achievements; that VASCEPA has been widely praised; and that VASCEPA is a commercial success.

The Court should accordingly find that Defendants infringe the Asserted Claims and that Defendants have not proven that those claims are invalid as obvious.

## **II. DEFENDANTS INDUCE INFRINGEMENT OF ALL ASSERTED CLAIMS**

Defendants seek FDA approval to market generic copies of VASCEPA as an adjunct to diet to reduce TG levels in adult patients with severe ( $\geq 500$  mg/dL) hypertriglyceridemia (the "MARINE indication"). Each Defendant's proposed labeling is—for purposes of the infringement analysis—identical to VASCEPA's label. PPF ¶ 228. Dr. Budoff's uncontroverted testimony at trial established that clinicians will perform the claimed methods when they treat severely hypertriglyceridemic patients with VASCEPA or one of Defendants' ANDA Products. PPF ¶¶ 358–60. (Defendants do not dispute they will induce clinicians to practice all but three categories of claim elements. Joint Stipulations of Fact ¶¶ 204–05, 216–17, 228–29 (ECF No. 324); PPF ¶¶ 361–496.) The remaining issue is whether Defendants *intend* that infringement occur, as is required to establish inducement liability. In Hatch-Waxman cases such as this one, courts determine whether defendants have the "specific intent, based on the contents of their proposed labels, to encourage physicians to use their proposed ANDA products" in a way that infringes the Asserted Claims. *Grunenthal GMBH v. Alkem Labs. Ltd.*, 919 F.3d 1333, 1339 (Fed. Cir. 2019) (citation omitted). The touchstone is whether the proposed generic labeling, taken in its entirety, encourages, recommends, promotes, or suggests an infringing use. PPF ¶ 290.

Defendants' non-infringement case largely amounts to rewriting Federal Circuit precedent. Contrary to Defendants' repeated assertions (*see, e.g.*, DPF ¶¶ 456–57, 578, 914), the proposed label need not "require" infringement. Rather "evidence that the product labeling that Defendants seek would inevitably lead *some* physicians to infringe establishes the requisite intent for inducement." *Eli Lilly & Co. v. Teva Parenteral Meds. Inc.*, 845 F.3d 1357, 1369 (Fed. Cir. 2017) (emphasis added); *see also Vanda Pharm. Inc. v. West-Ward Pharm. Int'l Ltd.*, 887 F.3d 1117,

1 1132 (Fed. Cir. 2018).<sup>1</sup> That standard is easily met here, notwithstanding Defendants’ assertion  
 2 that some physicians might prescribe EPA in a manner that would not infringe the Asserted Claims.

3 Defendants also contend that the existence of a substantial noninfringing use for a proposed  
 4 product precludes induced infringement. *See, e.g.*, DPF ¶ 572. That is wrong: “[T]here is no legal  
 5 or logical basis for th[is] suggested limitation on inducement.” *Sanofi v. Watson Labs. Inc.*, 875  
 6 F.3d 636, 646 (Fed. Cir. 2017); *see also Vanda*, 887 F.3d at 1133 (“[E]ven if the proposed ANDA  
 7 product has substantial noninfringing uses, West-Ward may still be held liable for induced  
 8 infringement.” (citation omitted)); *see also* MSJ Opinion at 8 (ECF. No. 278) (“Thus, . . .  
 9 contributory infringement can turn on whether there are substantial non-infringing uses, *while*  
 10 *inducement does not.*” (emphasis added)). Nevertheless, Defendants contend that because  
 11 substantial noninfringing uses exist, “induced infringement cannot be found here based on  
 12 labelling instructions that are merely *inferred.*” DPF ¶¶ 572, 573 n.11. Not so. In *AstraZeneca v.*  
 13 *Apotex*, for example, the generic labeling expressly instructed only twice-daily dosing, which the  
 14 generic argued was a substantial non-infringing use negating inducement (as the claims were  
 15 limited to once-daily dosing). The Federal Circuit rejected this argument and affirmed inducement.  
 16 633 F.3d 1042, 1057, 1059–60 (Fed. Cir. 2010). The label’s encouragement of “downward-titrate  
 17 to the lowest-effective dose” “would inevitably lead some consumers to practice the claimed  
 18 method.” *Id.* at 1057, 1060. In *Sanofi*, even when 23% of prescriptions were noninfringing, *see*  
 19 875 F.3d at 645, the court found “the content of the label . . . permits the inference of specific  
 20 intent to encourage the infringing use.” *Id.* at 646.

21 **A. Defendants Intend to Induce Clinicians to Prescribe Their Respective ANDA**  
 22 **Products for at Least 12 Weeks**

23 The evidence shows that Defendants’ proposed labeling will encourage clinicians to  
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25 <sup>1</sup> Defendants also cite *Depomed* for the proposition that there was no induced infringement when  
 26 5% of the uses were non-infringing. DPF ¶ 458. But the discussion in *Depomed* that Defendants  
 27 cite specifically discussed *contributory* infringement, where the existence of a substantial non-  
 28 infringing use is a defense.

1 administer EPA to patients for at least 12 weeks.

2       *First*, the indication itself encourages clinicians to prescribe for the long-term to reduce  
3 TGs *and maintain that reduction*—an understanding both sides’ experts confirmed. PPF ¶ 298–  
4 99. Reducing TGs *and* maintaining that reduction requires long-term therapy in the vast majority  
5 of patients, both because severe hypertriglyceridemia is often chronic and because lifestyle  
6 changes that might allow a patient to stop drug therapy take a long time. PPF ¶¶ 301–04; *see also*  
7 PPF ¶ 301 (FDA recognized VASCEPA would be administered chronically); PPF ¶ 303 (80% of  
8 severely hypertriglyceridemic patients require long-term treatment); DPF ¶ 106 (same).

9       *Second*, the Dosage and Administration section encourages clinicians to prescribe for long-  
10 term use. PPF ¶¶ 306–08. Section 2.1, entitled “Prior to Initiation of Icosapent Ethyl,” instructs  
11 clinicians to first manage other causes of very high TGs like underlying medical conditions,  
12 medications, nutritional intake, and lack of physical activity. PPF ¶ 307. That some clinicians may  
13 ignore these instructions, *see* DPF ¶ 611, is beside the point: “In the context of specific intent, it is  
14 irrelevant that some users may ignore” statements in the proposed labeling. *AstraZeneca*, 633 F.3d  
15 at 1060. Initiating VASCEPA without first taking the steps in Section 2.1 would be an off-label  
16 use. PPF ¶ 308. Moreover, as is common with drugs used for chronic administration, the section  
17 does not limit the duration of treatment. PPF ¶ 316.

18       *Third*, the Clinical Studies section reports the effects of a 12-week course of therapy on the  
19 lipid profile of severely hypertriglyceridemic patients. PPF ¶¶ 309–13. The labeling thus provides  
20 a benchmark for evaluating patient response at 12 weeks; no earlier timeframe is provided. PPF  
21 ¶¶ 310–11. Clinicians read this section as more than just a description of a study. The experts agree  
22 that it serves to facilitate the safe and effective use of the drug by showing that it is safe and  
23 effective for maintaining TG reductions over the long-term. PPF ¶¶ 309–10.

24       Defendants argue that their labeling does not induce 12-week administration because short-  
25 term use is not expressly excluded from the labeling, and because severe hypertriglyceridemia is  
26 not *necessarily* a chronic condition but may *sometimes* be caused by transient factors. *See, e.g.*,  
27 DPF ¶¶ 572–82. This simply repackages their substantial noninfringing use argument. The record  
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1 makes clear that *many* patients will require long-term treatment for severe hypertriglyceridemia.  
2 PPF ¶¶ 303–04. The label is directed to treat patients with chronic conditions, encouraging  
3 clinicians *not* to administer drug therapy until acute phenomena are addressed. PPF ¶¶ 306–08.  
4 This more than suffices to establish inducement. *See, e.g., Sanofi v. Glenmark Pharm. Inc., USA*,  
5 204 F. Supp. 3d 665, 684 (D. Del. 2016), *aff’d sub nom. Sanofi v. Watson Labs. Inc.*, 875 F.3d 636  
6 (Fed. Cir. 2017) (intent to induce administration for at least 12 months based on “additional clues  
7 in the labels . . . suggest[ing] long-term treatment” and “the experts’ testimony that prescribing  
8 physicians generally intend to treat patients . . . for longer than [claimed.]”); PPF ¶ 283.

9 Defendants’ contrary argument relies on three cases: *HZNP Medicines LLC v. Actavis*  
10 *Laboratories UT, Inc.*, 940 F.3d 680 (Fed. Cir. 2019) (“*Horizon*”), *Grunenthal GmbH v. Alkem*  
11 *Laboratories Ltd.*, 919 F.3d 1333 (Fed. Cir. 2019), and *Takeda Pharmaceuticals U.S.A., Inc. v.*  
12 *West-Ward Pharmaceutical Corp.*, 785 F.3d 625 (Fed. Cir. 2015). DPF ¶¶ 583–87. The Court’s  
13 summary judgment ruling already identified several decisive differences between those cases and  
14 this one. MSJ Opinion at 10–11 & n.4 (ECF No. 278). In those cases, the patent holders were  
15 trying to bootstrap inducement from vague statements in the labels. For example, in *Horizon*, the  
16 patented method required three steps, but the drug was approved and hence found safe and  
17 effective only for the first step (topical treatment). *Horizon*, 940 F.3d at 699–700. The only  
18 statement in the label touching on the other two steps was a warning about how to add additional  
19 topical medicaments if the patient so desired. *Id.* at 702. Nothing in the label encouraged clinicians  
20 or patients to *actually use* these additional topical medicaments. *Id.*; *see also* MSJ Opinion at 10  
21 n.4 (ECF No. 278). Here, Amarin relies not on warnings explaining how *not* to use the drug, but  
22 rather on the approved use itself: a condition recognized as typically chronic, as requiring long-  
23 term administration, and for which the supporting clinical evidence featured 12-week  
24 administration.

25 *Grunenthal* and *Takeda* are also distinguishable. Both cases involved labeling that omitted  
26 (carved out) the patented indication. *Grunenthal*, 919 F.3d at 1339–40; *Takeda*, 785 F.3d at 630–  
27 32. These carve-outs left the patent holders clinging to general statements that did not encourage  
28

1 treatment of the specific condition that was the subject of the claimed methods. *Grunenthal*, 919  
 2 F.3d at 1339–40; *Takeda*, 785 F.3d at 630–632. The other cases Defendants cite are similarly  
 3 inapposite. *See, e.g., Otsuka Pharm. Co. v. Torrent Pharm. Ltd., Inc.*, 99 F. Supp. 3d 461, 490  
 4 (D.N.J. 2015) (“fleeting references” in the warnings sections of the defendants’ labels were  
 5 insufficient in the face of a carve-out); *United Therapeutics Corp. v. Sandoz Inc.*, No. 12-CV-  
 6 01617, 2014 WL 4259153, at \*21 (D.N.J. Aug. 29, 2014) (defendant carved out the patented use  
 7 and included “explicit, non-infringing instructions”). None of these cases support Defendants’  
 8 assertion that accused labeling must require only infringing uses and rule out noninfringing ones;  
 9 it is enough that the labeling encourages, recommends, promotes or suggests the infringing use,  
 10 leading some clinicians to practice the claimed method in some patients. PPF ¶ 292; *see also*  
 11 *Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d 566, 587 (D. Del.  
 12 2018) *aff’d sub nom. Persion Pharm. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184 (Fed.  
 13 Cir. 2019) (Bryson J.) (rejecting assertion that labeling must require the infringing use in order to  
 14 induce the use).

15 **B. Defendants Intend to Induce Clinicians to Prescribe Their Respective ANDA**  
 16 **Products to Achieve The Claimed Lipid Effects**

17 The evidence also shows that the labeling will encourage clinicians to use EPA to effect  
 18 (1) a reduction in TGs in severely hypertriglyceridemic patients that is statistically significant, or  
 19 of at least 10% or 20% (PPF ¶¶ 320, 432, 453, 470), while (2) also achieving the additional benefits  
 20 of avoiding LDL-C increases (PPF ¶¶ 320, 322), and/or (3) reducing apo B (PPF ¶¶ 320, 339).  
 21 These effects occurred in the substantial majority of patients in MARINE, with the 12-week results  
 22 reported in the Clinical Studies section of Defendants’ proposed labels. *See, e.g.*, PPF ¶¶ 326–28.  
 23 Defendants’ attempt to discount the Clinical Studies is unconvincing.

24 First, Defendants dispute the relevance of the Clinical Studies section, which they assert is  
 25 often ignored by clinicians who have no way of knowing whether the lipid effects reported in the  
 26 label will be achieved in a particular patient. *See* DPF ¶¶ 194–97. The record says otherwise. Both  
 27 sides’ experts acknowledged the significance of the clinical study data to clinicians, and  
 28

1 Defendants’ own regulatory expert acknowledged that the Clinical Studies section of the labeling  
2 is specifically drafted by FDA to facilitate safe and effective use of the drug and call out the  
3 information “important to clinical decision making.” PPF ¶ 326; *see also* PPF ¶ 351; Trial Tr.  
4 352:2–354:4 (Budoff Direct) (Clinical Studies section changed clinicians’ prescribing practices).  
5 The Clinical Studies section describes the relevant clinical outcomes in a majority of patients,  
6 allowing and encouraging clinicians to prescribe with the intent and expectation of achieving the  
7 described lipid effects. *See* PPF ¶¶ 333–34, 341. It is absurd to suggest, as Defendants do, that the  
8 Clinical Studies section is a “mere description,” unconnected to a clinician’s expectations in  
9 administering a drug. Noticeably absent from the trial record is any explanation of where a  
10 clinician’s expectations about a drug’s effects would come from, if not from the Clinical Studies  
11 section of the drug labeling.

12 Federal Circuit Judge Bryson, sitting by designation in the district court, recently rejected  
13 a similar attempt to denigrate informational portions of a drug’s labeling (in that case, the  
14 Pharmacokinetics section). He rejected as “conclusory” and “not . . . credible” expert testimony  
15 downplaying the Pharmacokinetics section as “simply stating data without commentary” that does  
16 not promote a drug’s use to achieve the described effects. *See Pernix*, 323 F. Supp. 3d at 585–86  
17 (D. Del. 2018) (Bryson, J.) (data in the Pharmacokinetics section and testimony about the  
18 importance of that section to clinicians established intent to induce claim limitations requiring that  
19 certain parameters would not increase by more than 14% or 30%).

20 Second, Defendants incorrectly assert that intent to induce can be shown only if the  
21 Indication and Usage section contains the specific lipid effects described in the Asserted Claims  
22 (for example, if the indication was to reduce TGs by 20%, not just to reduce TGs). *See, e.g.*, DPF  
23 ¶¶ 192, 199. Defendants’ approach conflicts with FDA guidance—according to FDA, this section  
24 need only “*concisely* describe[] the condition or disease that the drug is intended to benefit.” Trial  
25 Tr. 1328:17–20 (Peck Direct) (emphasis added). It is well-established that information contained  
26 within the entire label, including the Clinical Studies section, must be considered when analyzing  
27 intent to induce. *See, e.g., Bayer Schering Pharma AG v. Lupin Ltd.*, 676 F.3d 1316, 1324 (Fed.  
28

1 Cir. 2012) (considering whether “the label, taken in its entirety, [] recommend[s] or suggest[s] to  
 2 a physician that [the product] is safe and effective for inducing the claimed combination of effects  
 3 in patients”); *Sanofi*, 875 F.3d at 645 (relying in part on Clinical Studies section).<sup>2</sup>

4 *TG Reduction.* Nobody disputes that the labeling encourages the administration of EPA to  
 5 effect a reduction in TGs. Joint Stipulations of Fact ¶¶ 200, 212, 224 (ECF No. 324) (products are  
 6 indicated to reduce TGs in severely hypertriglyceridemic patients); *see also* PPF ¶¶ 321, 323. The  
 7 Clinical Studies section also encourages clinicians to prescribe EPA with the intent to achieve  
 8 specific magnitudes of TG reductions.<sup>3</sup> Table 2 informs clinicians that in the MARINE study, most  
 9 patients achieved a reduction in TGs of 33% compared to placebo and 27% compared to baseline,  
 10 both greater than 10% and 20%, and reports a p-value of less than 0.001, indicating statistical  
 11 significance. PX 1186 (VASCEPA Label) at 11; PPF ¶¶ 189, 433, 454–58, 471–74. Upon review,  
 12 clinicians expect similar results in most of their patients. Similar TG reductions do in fact occur in  
 13 most patients treated by both parties’ clinicians. PPF ¶¶ 334, 459.

14 *Maintain LDL-C.* The labeling likewise encourages clinicians to prescribe EPA to reduce  
 15 TGs with the expectation that their patients will enjoy the additional benefit of not raising LDL-  
 16 C.<sup>4</sup> The Dosage and Administration section instructs clinicians to “[a]ssess lipid levels before  
 17 initiating therapy.” PX 1186 (VASCEPA Label) at 2; PPF ¶ 324. Part of this assessment is a  
 18

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19 <sup>2</sup> Defendants also argue that the Clinical Studies section is only relevant where the Indication and  
 20 Usage section expressly cross references it. But Defendants’ own regulatory expert acknowledged  
 21 that the function and significance of the Clinical Studies section remains the same, regardless of  
 22 whether a cross-reference is included in the Indication. Mathers Dep. 178:8–24. Cross-references  
 23 are used only when the Clinical Studies section explains a limitation of use in the Indication  
 24 section, rather than in the Indication as a whole. *Id.* at 177:18–178:7. Here, the Clinical Study  
 25 section is relevant to the entirety of the indication. *Id.* at 188:5–189:5.

26 <sup>3</sup> Depending on the claim, this TG reduction is 10%, 20% or statistically significant: ’715 Patent,  
 27 Claim 14 (statistically significant); ’560 Patent, Claim 4 (10%); ’560 Patent, Claim 17 (20%).

28 <sup>4</sup> Depending on the claim, the LDL-C claim language differs slightly: ’728 Patent, Claims 1 and  
 16 (“without substantially increasing LDL-C”); ’715 Patent, Claim 14 (“without effecting a  
 26 statistically significant increase in LDL-C”); ’677 Patent Claims 1 and 8, ’652 Patent Claim 1  
 (“without substantially increasing LDL-C”); ’560 Patent Claim 4 (“without increasing LDL-C by  
 27 more than 5%”); ’560 Patent Claim 17 (“without increasing LDL-C”).

1 patient's LDL-C level. PPF ¶ 325. While TGs are central to treatment of severe  
2 hypertriglyceridemia, attention to other lipids is important and called out in the Clinical Study  
3 section. Trial Tr. 404:5–405:1 (Budoff Direct). Clinicians look to the Clinical Studies section to  
4 inform their clinical decision-making. PPF ¶¶ 325–26. Notably, the language beneath Table 2  
5 expressly calls out to clinicians that “[t]he reduction in TG observed with icosapent ethyl was not  
6 associated with elevations in LDL-C levels relative to placebo.” PPF ¶¶ 326–27. Table 2 itself  
7 reports that severely hypertriglyceridemic patients experienced a 5% reduction in LDL-C  
8 compared to baseline and a 2% reduction compared to placebo. PX 1186 (VASCEPA Label) at  
9 11. These median results are important to doctors because, as Dr. Budoff testified, “doctors can  
10 expect similar results in a majority of individual patients.” Trial Tr. 511:22–512:2 (Budoff Cross).  
11 This LDL-C data is particularly relevant here—it was (before REDUCE-IT) the key distinguishing  
12 feature over other approved TG-lowering medications. PPF ¶¶ 330–32.

13 Defendants further argue that they cannot be found to induce infringement of this limitation  
14 because using VASCEPA to achieve the claimed LDL-C effects is, they assert, not an “approved  
15 use” of VASCEPA. DPF ¶¶ 200–204, 946. Defendants’ assertion is remarkable given that both  
16 sides’ regulatory experts testified that administering the drug to reduce TGs without raising LDL-  
17 C is an approved use of the drug. PPF ¶ 335. FDA too has made clear that Defendants are wrong  
18 about the scope of approval. PPF ¶ 335 (FDA-reviewed advertisements promoting use of  
19 VASCEPA to reduce TGs without raising LDL-C). In any event, that the beneficial effect on LDL-  
20 C is not set forth in the Indication itself is not an impediment to induced infringement, which is  
21 judged on the basis of the labeling as a whole. *Bayer*, 676 F.3d at 1323–24; PPF ¶¶ 284 291–92;  
22 *see also* MSJ Opinion at 14–15 (ECF No. 278).

23 *Apo B Reduction.* For many of the same reasons described above with respect to the  
24 claimed LDL-C effects, the label—considered as a whole—encourages, recommends, promotes,  
25  
26  
27  
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1 or suggests to clinicians that they administer the drug to reduce both TGs and apo B.<sup>5</sup> The labeling  
2 conveys to clinicians both the clinical significance of the apo B reduction and that it will occur in  
3 most patients. PPF ¶¶ 338–42. The Clinical Studies section instructs that “VASCEPA 4 grams per  
4 day reduced median TG. . . and Apo B levels from baseline relative to placebo.” PX 1186  
5 (VASCEPA Label) at 11. Table 2 specifies that severely hypertriglyceridemic patients’ apo B  
6 levels were significantly reduced by 9% compared to placebo and 4% compared to baseline. *Id.*

7 Defendants appear to believe that there can be no induced infringement because some  
8 clinicians may find the apo B data in the label irrelevant to their clinical practice. However, by  
9 including the apo B data, the Clinical Studies section identifies apo B as among the “relevant  
10 parameters to measure on a routine basis and to monitor.” Mathers Dep. 134:10–22. Indeed, both  
11 parties’ experts testified about the importance of apo B levels when treating severely  
12 hypertriglyceridemic patients. Defendants’ clinical expert, Dr. Sheinberg, regularly tests his  
13 severely hypertriglyceridemic patients’ apo B levels, and doing so is an important part of his  
14 practice. PPF ¶ 341; Trial Tr. 658:6–22 (Sheinberg Cross). Dr. Budoff, on the other hand, does not  
15 generally impose the cost of an apo B lab test on his patients, but he nevertheless expects his  
16 severely hypertriglyceridemic patients’ apo B to decrease when treated with VASCEPA. *See* PPF  
17 ¶ 339; *see also* Trial Tr. 542:14–24 (Budoff Re-Direct) (expects patients to follow the general  
18 results of the MARINE trial, including a decrease in apo B). Finally, for similar reasons to the  
19 claimed LDL-C effects, the apo B claim elements are not directed to off-label use; the recitation  
20 of this generally beneficial additional effect is not a hurdle to a finding of induced infringement.  
21 *See Bayer*, 676 F.3d at 1323–24; *see also* MSJ Opinion at 14–15 (ECF No. 278).<sup>6</sup>

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23 <sup>5</sup> Depending on the claim, the apo B reduction claim language also differs slightly: ’715 Patent,  
24 Claim 14 (“to effect a statistically significant reduction in . . . apolipoprotein B”); ’677 Patent,  
25 Claim 8 (“to effect a reduction in apolipoprotein B”); ’929 Patent, Claim 5 (“effective to reduce  
apolipoprotein B”).

26 <sup>6</sup> Defendants also argue that, because FDA did not approve the ANCHOR indication, which  
27 included language about apo B in the Indications and Usage section of the label, the current label  
28

**C. Defendants Intend to Induce Administration “Without Concurrent Lipid Altering Therapy”**

Defendants are seeking approval for—and their labeling encourages—use of EPA as monotherapy without concurrent medication. The Indications and Usage section instructs clinicians that EPA is approved as monotherapy (as an adjunct to diet, without concurrent administration of any other medication). PPF ¶ 346. If EPA were safe and effective *only* when used with a concurrent lipid altering therapy, the Indication and Usage section would say so. PPF ¶ 347. Likewise, the Dosage and Administration section does not specify any medication to be used in combination with EPA and the clinician would understand from this, and the remainder of the labeling (including the Clinical Studies section) that the drug was approved as safe and effective as monotherapy. PPF ¶¶ 349–53. The labeling thus encourages or recommends administration of VASCEPA either as monotherapy or co-administered with a concurrent lipid altering therapy, like a statin, depending on a given patient’s characteristics. *See* Trial Tr. 411:5–414:15 (Budoff Direct). It therefore is wrong to conclude, as Defendants do, that the labeling encourages *neither* administration as monotherapy *nor* in combination. *See, e.g.*, DPF ¶¶ 913–14.

The Federal Circuit has disagreed with Defendants’ position in analogous circumstances. The patent claims in *Sanofi v. Watson* were directed only to a combination therapy, but the label demonstrated that the drug was safe and effective as either monotherapy or in combination. 875 F.3d at 645 n.2. Relying on the information about the clinical trial in the Clinical Studies section, the Federal Circuit affirmed the district court’s induced infringement finding. *Id.*; *see also Sanofi v. Glenmark*, 204 F. Supp. 3d at 683 (based on the description of patients on combination therapy and monotherapy in the clinical studies section, concluding that “[d]efendants knew that their

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must not express FDA approval of the additional benefit of reducing apo B in the severely hypertriglyceridemic. *See* DPF ¶ 218. This argument has no merit, as the ANCHOR indication was directed to an entirely different patient population, those with mixed dyslipidemia, and its rejection by FDA reflected the then prevailing skepticism concerning the cardiovascular benefits of TG-lowering medication generally, and not doubt about the lipid effects proved in MARINE in treating severe hypertriglyceridemia. Trial Tr. 117:10–25; 126:13–127:16 (Ketchum Direct).

proposed labels would inevitably lead some physicians to administer [the drug in combination therapy]” (citation omitted)).

The same is true here. Defendants’ labeling encourages, recommends, promotes, or suggests to clinicians that they should prescribe EPA as monotherapy in cases where a patient does not need concurrent lipid altering therapy. These statements “will inevitably lead some physicians” to administer EPA without concurrent lipid altering therapy.

### **III. DEFENDANTS HAVE NOT MET THEIR BURDEN OF PROVING THAT THE ASSERTED CLAIMS WERE OBVIOUS**

Defendants contend that the POSA would have been motivated by the experience with Lovaza—in which LDL-C rose dramatically in patients with severe hypertriglyceridemia—to substitute the substantially pure EPA used in Mori 2000 for the EPA-DHA mixture in Lovaza with a reasonable expectation that there would be no undesirable increase in LDL-C. DPF ¶ 645. But Defendants have not come close to showing by clear and convincing evidence that the claimed invention was obvious. They failed to show (1) that the POSA would have reasonably expected that high purity EPA would lower TGs without substantially increasing LDL-C in patients with severe hypertriglyceridemia; (2) that the POSA would have been motivated to substitute EPA for the EPA-DHA mixture in Lovaza; (3) that the POSA would have found it “obvious to try” EPA for treating severe hypertriglyceridemia; and (4) that the powerful objective indicia of non-obviousness should be disregarded. PPF ¶¶ 497–905. These failings are addressed below.

#### **A. Defendants Have Not Shown That a POSA Would Have Reasonably Expected Success With an EPA Formulation**

Defendants did not show, let alone by clear and convincing evidence, that a POSA would have reasonably expected success in lowering TGs without concomitantly raising LDL-C in a severely hypertriglyceridemic population using an EPA formulation. PPF ¶¶ 704–19, 837–53.

*First*, the POSA would have understood that *all* TG-lowering drugs approved to treat severe hypertriglyceridemia dramatically increased LDL-C: this was true of niacin, fibrates, and omega-3-fatty acids. PPF ¶¶ 33–53, 659–67, 681. This was understood to be a “*general*

phenomenon”—inherent in the way these drugs lowered TGs in the severely hypertriglyceridemic, through conversion of VLDL to LDL. PPF ¶¶ 41–49. Critically, the dramatic increase in LDL-C observed when these drugs were administered to the severely hypertriglyceridemic occurred even though when *the very same drugs* were administered to patients with less elevated TGs, there was no substantial increase in LDL-C: either LDL-C did not rise to a significant degree (Lovaza) or even went down (fibrates). PPF ¶¶ 49–53, 509. Defendants provide no plausible reason, let alone a clear and convincing one, why the POSA would have disregarded this body of experience and understanding, or expected to see anything different with EPA, an omega-3-fatty acid. To the contrary, EPA was understood to reduce TGs in just the way fibrates and Lovaza’s EPA-DHA mixture did—through enhanced clearance of VLDL—indicating that LDL-C would rise with EPA alone, just as it had with the prior TG-lowering agents. PPF ¶¶ 42–47; *see also* PX 486 (Bays 2008) at 9 (“Specifically, EPA and DHA may increase LPL [lipoprotein lipase] activity, and thus, increase [lipoprotein lipase]-mediated clearance of TRL [triglyceride rich lipoproteins (*i.e.*, VLDL and IDL)].”).

*Second*, Defendants’ references say nothing about the expected effect of EPA on LDL-C in patients with *severe hypertriglyceridemia*. While Defendants principally rely on Mori to assert that there was a reasonable expectation of success, the POSA would have understood that Mori addressed the *mildly* hypertriglyceridemic population (with only slightly elevated TGs), rather than the *severely* hypertriglyceridemic population (with TGs  $\geq$  500 mg/dL). PPF ¶ 683. Indeed, the population studied in Mori was most like the mixed dyslipidemic population in the Tricor label—which experienced a *decrease* in LDL-C. PPF ¶¶ 509–10, 550. That Defendants principally rely on Mori, even though it studied the wrong population and touted the benefits of DHA rather than EPA, is telling: as Dr. Heinecke admitted, “I don’t think there’s *any* evidence in the prior literature about what the impact of EPA would be on LDL cholesterol in [the severely hypertriglyceridemic].” PPF ¶ 508. Of course, plenty of literature and decades of experience does bear on the question, but all of it taught that LDL-C would dramatically increase in severely hypertriglyceridemic patients. Defendants ignore that consistent teaching and cite to inapposite

1 references—including not only Mori, but also Hayashi (mean of 300) and Kurabayashi (mean of  
2 136)—which reported on administration of EPA in patients with TG levels far below 500. PPF  
3 ¶¶ 549–82. These references have nothing to say about patients with *severe hypertriglyceridemia*,  
4 and would not have provided the POSA with any reason to expect that EPA would avoid the large  
5 LDL-C increases observed with all approved severe hypertriglyceridemia treatments. PPF ¶¶ 549–  
6 82, 704–18, 837–49.

7 *Third*, even in patients with TGs *below* 500 mg/dL, the prior art taught that EPA raised  
8 LDL-C. While Mori reported that the LDL-C *increase* with EPA was not statistically significant  
9 in that small study (in the wrong population), it was but one of many articles studying the lipid  
10 effects of omega-3-fatty acids. When that prior art is considered *as a whole*, it is clear that it did  
11 not distinguish between DHA and EPA based on their effects on LDL-C. PPF ¶¶ 684–91. And  
12 when a review article—by von Schacky—surveyed and synthesized that literature, it found that  
13 *both* DHA and EPA raised LDL-C, and to a similar degree. PPF ¶¶ 688–691. Indeed, that the prior  
14 art did not teach the benefits of EPA alone for severe hypertriglyceridemia is confirmed by real-  
15 world evidence: more than a decade after purified EPA was available in Japan, GlaxoSmithKline  
16 and Reliant developed the Lovaza mixture, not EPA, for treatment of severe hypertriglyceridemia  
17 and, even then, no one suggested removing the DHA to achieve a better outcome. PPF ¶ 503.

18 Faced with this compelling evidence, Defendants rely on a mischaracterization of the law  
19 of obviousness—contending that they are not required to show a reasonable expectation of success  
20 because the Asserted Patents do not themselves present clinical data showing that LDL-C did not  
21 substantially rise when the claimed method is practiced. DPF ¶¶ 727–39. But the cases they rely  
22 upon—*Merck & Co. v. Teva Pharmaceuticals USA*, 395 F.3d 1364 (Fed. Cir. 2005), *Alcon*  
23 *Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362 (Fed. Cir. 2012), *Hoffmann-La Roche Inc. v. Apotex*  
24 *Inc.*, 748 F.3d 1326 (Fed. Cir. 2014), and *In re Copaxone Consolidated Cases*, No. CV 14-1171-  
25 GMS, 2017 WL 401943 (D. Del. Jan. 30, 2017)—do not purport to overrule the long-standing  
26 requirement that obviousness may be found only where a reasonable expectation of success has  
27 been shown (PPF ¶¶ 512, 756) and are inapposite for other reasons as well. *See generally* PPF  
28

¶¶ 755–61.

In these cases, the patent holder attempted to denigrate prior art suggesting the claimed invention by pointing to a lack of proof also absent from the patent itself. Here, by contrast, nothing in the prior art suggested using purified EPA to treat severe hypertriglyceridemia—only the patents teach the clinical benefits of doing so. PPF ¶¶ 508, 758–59. Thus, in this case, unlike those relied upon by Defendants, the patents dramatically *add* to what was disclosed in the prior art—specifically teaching a new way of treating severe hypertriglyceridemia and describing its clinical benefits, and then confirming those benefits during the prosecution by submission of the MARINE results. PPF ¶¶ 759–60. None of Defendants’ cases suggest that because the MARINE results were submitted to the Patent Office during prosecution rather than as part of the patent specifications, the Court should dispense with the mandated reasonable expectation of success inquiry. PPF ¶¶ 756–61. To the contrary, the Patent Office has instructed, and the Federal Circuit has confirmed, that clinical study results need not be included in a patent application, and can properly be submitted during prosecution. *Amarin Reply in Support of Motion for Partial SJ* at 2–3, ECF No. 264. And the Federal Circuit has repeatedly made clear that an obviousness challenge must overcome all unexpected benefits of the invention, regardless of when they become known. *See, e.g., Sanofi–Aventis Deutschland GmbH v. Glenmark Pharm. Inc., U.S.A.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014) (“Glenmark also argues that later-discovered benefits cannot be considered in an obviousness analysis, here referring to the improved kidney and blood vessel function that were observed after the patent application was filed. That is incorrect; patentability may consider all of the characteristics possessed by the claimed invention, whenever those characteristics become manifest.”). Thus, while it is unsurprising that Defendants seek to avoid having to prove that the POSA would somehow have *expected* EPA to defy the outcome seen in every prior-art TG-lowering product approved for severe hypertriglyceridemia by avoiding LDL-C increases, the law does not allow the invalidation of an issued patent so readily.

Defendants also argue that the prior art concerning how Lovaza, fibrates and niacin performed in the severely hypertriglyceridemic would not have informed the expectation as to how

1 EPA would perform in the same population. DPF ¶¶ 751–58. But all approved TG-lowering drugs  
 2 were understood to work in the same way—by increasing conversion of VLDL to LDL particles—  
 3 and no prior art suggested that EPA by itself would operate differently, or was not subject to the  
 4 “general phenomenon” of raising LDL-C in the severely hypertriglyceridemic. PPF ¶¶ 39–53,  
 5 704–71, 837–41. To the contrary, the prior art described EPA as operating in precisely the same  
 6 way as all of the other TG-lowering agents. *See* PX 486 (Bays 2008) at 9 (“Specifically, EPA and  
 7 DHA may increase LPL [lipoprotein lipase] activity, and thus, increase [lipoprotein lipase]-  
 8 mediated clearance of TRL [triglyceride rich lipoproteins (*i.e.*, VLDL and IDL)]”) and at 12 (“The  
 9 reason for the increased LDL-C levels with omega-3-fatty acids is related to the increased  
 10 conversion of VLDL particles to LDL particles.”).<sup>7</sup> This is fatal to Defendants’ obviousness case.<sup>8</sup>

11 Defendants also irrelevantly argue that none of the prior art concerning niacin, fibrates, or  
 12 omega-3-fatty acids “criticized, discredited, or otherwise discouraged” using EPA to lower TGs  
 13 in the severely hypertriglyceridemic. DPF ¶ 752. But Defendants are attacking a straw man: the  
 14 question is not whether the prior art expressly disparaged EPA, but whether it provided a  
 15 reasonable expectation that EPA—unlike the previously approved TG-lowering agents for the  
 16 severely hypertriglyceridemic—would avoid substantially increasing LDL-C. It did not.

17 Nor do Defendants advance their defense by attempting to focus on a hypothetical patient  
 18 with TG levels of precisely 500 mg/dL. DPF ¶ 754. Even assuming such a patient existed, 500  
 19 mg/dL is the established threshold for the very high TG population, and the prior art taught that  
 20 this population was subject to large LDL-C increases. PPF ¶¶ 662, 667. It did not suggest that  
 21 \_\_\_\_\_

22 <sup>7</sup> Bays 2008 (PX 486) made these observations fully aware of the Mori 2000 reference (DX 1538)  
 23 relied upon by Defendants. *See* PX 486 (Bays 2008) at 18, n. 174. Bays 2008 thus further confirms  
 24 that Mori did not teach that EPA and DHA differ with respect to their TG-lowering mechanisms,  
 or their effects on LDL-C levels.

25 <sup>8</sup> Desperate to find support for their position, Defendants mischaracterize Dr. Toth’s testimony as  
 26 providing that EPA and DHA would be expected to perform differently with respect to LDL-C  
 27 effects. DPF ¶¶ 267, 304, 318. Dr. Toth was referring to other effects, however. PPF ¶¶ 553–62,  
 673–80. With respect to LDL-C, he testified—consistent with the prior art—that DHA and EPA  
 would have been understood to have the same effects. Trial Tr. 1665:17–1669:16 (Toth Direct).

1 patients with TGs of exactly 500 mg/dL would avoid substantial LDL-C increases; instead, it  
2 taught that substantial increases were observed with TG-lowering agents even at 400 mg/dL. PPF  
3 ¶ 709 (“In patients with more marked hypertriglyceridemia (*e.g.*, 400 to 1000 mg/dL) . . . LDL  
4 increases of 10% to 30% are seen frequently.”). Finally, that the populations studied for Tricor and  
5 Lovaza had mean TG levels of 726 and 816 mg/dL (DPF ¶ 751) is immaterial as any patient  
6 *population* with severe hypertriglyceridemia will have a mean TG level that exceeds 500 mg/dL.

7 Without legal support to dispense with part of the obviousness inquiry and without prior  
8 art providing a basis to find a reasonable expectation of success, Defendants attempt to rely on  
9 Amarin documents to try to prove their case. DPF ¶¶ 743–47. Not only do many of those  
10 documents post-date the invention (obviousness is assessed *at the time of the invention*), but the  
11 documents reflect the views of the *inventors*, whose thoughts are not relevant to the obviousness  
12 analysis. PPF ¶¶ 744–54. When Amarin solicited views of *outside* experts, those experts expressed  
13 the same view that a POSA would have held—that with EPA treatment in the severely  
14 hypertriglyceridemic, “LDL-C is likely to go up as it does with virtually all TG-lowering  
15 therapies.” PPF ¶ 838. And von Schacky, which reviewed the prior art wholly independently of  
16 Amarin, reached the same conclusion, showing both EPA and DHA as raising LDL-C. PPF  
17 ¶¶ 607–08.

18 Defendants also attempt to paper over the gaping holes in their obviousness attack by  
19 asserting that the prior art must teach the claimed invention because it is the prior art (they say)  
20 that the inventors relied upon in conceiving their invention. This is wrong both in fact and law. As  
21 to the facts, named inventor Dr. Manku testified that the invention was premised upon proprietary  
22 clinical data from trials sponsored by Amarin (and its predecessor Laxdale) in neuropsychiatric  
23 disorders. PPF ¶ 63. That data helped elucidate the biochemical effects of EPA and showed the  
24 inventors—a teaching absent from the prior art—that DHA appeared to interfere with the effects  
25 of EPA, leading to their insights concerning the clinical benefits of purified EPA. PPF ¶ 63. While  
26 Defendants quote approvingly from Dr. Bays’s testimony that named inventor Dr. Soni told him  
27 that conception was based on the effects of EPA seen in “studies of patients who did not have very  
28

1 high triglycerides,” DPF ¶ 253 (quoting Bays Dep. 37:9–20), they fail to acknowledge that the  
2 studies Dr. Soni was referencing were Amarin’s studies in neuropsychiatric patients, not the prior  
3 art studies upon which Defendants’ obviousness case depends. *See* Bays Dep. 35:23–36:12.  
4 Defendants’ own validity expert conceded that the inventors’ reliance on these studies was  
5 contrary to the conventional wisdom and outside the understanding of a POSA. PPF ¶ 64.

6 As to the law, Section 103 of the Patent Code expressly provides that “[p]atentability shall  
7 not be negated by the manner in which the invention was made.” 35 U.S.C. § 103. Defendants’  
8 attack on how the inventors made their invention is thus contrary to law, as well as fact. *See Sanofi-*  
9 *Aventis Deutschland GmbH*, 748 F.3d at 1360 (“Technologic advance flows from knowledge,  
10 experience, insight—perhaps hunch or curiosity. Patentability does not turn on how the invention  
11 was made, but on whether it would have been obvious to a person of ordinary skill in the field.”).

12 Finally, Defendants rely upon statins to argue that the POSA would not have concluded  
13 that all TG-lowering drugs raised LDL-C. DPF ¶¶ 761–64. But despite the unequivocal testimony  
14 of both Drs. Heinecke and Toth that statins were not approved for treatment of severe  
15 hypertriglyceridemia (PPF ¶ 740), and ATP-III’s statement that statins are not appropriate for use  
16 as a “first line agent for very high triglycerides” because they are “not powerful triglyceride-  
17 lowering drugs” (PPF ¶ 742), Defendants quibble, arguing that statins had been studied in patients  
18 with “Frederickson Type IV,” which included *some* patients with TGs over 500 mg/dL (DPF  
19 ¶ 763). But statins had not been studied in Frederickson Type V—which would have been required  
20 to obtain approval for treating severe hypertriglyceridemia. PPF ¶ 740. Moreover, the portion of  
21 the Lipitor label Defendants point to (1) does not distinguish between patients with TG levels  
22 below and above 500 mg/dL, so there is no way to assess Lipitor’s effect on those patients with  
23 severe hypertriglyceridemia, and (2) shows that some patients experienced very large *increases* in  
24 TGs—clearly undesirable in a TG-lowering agent for severe hypertriglyceridemia. PPF ¶ 741.

25 Moreover, the prior art taught that to the extent statins reduced TGs, they did so through  
26 an entirely different mechanism of action than niacin, fibrates, and omega-3-fatty acids, and  
27 therefore would not have been viewed by a POSA as relevant to EPA. PPF ¶ 743. Not surprisingly,  
28

Dr. Heinecke did not even rely on the Lipitor label as a prior art reference, so Defendants cannot cite to his testimony to support their eleventh-hour assertions—made despite the strictures of 35 U.S.C. § 282(c). *See* PPF ¶¶ 736–38. Aside from not having to address the lack of evidence that Lipitor was known to treat severe hypertriglyceridemia effectively, Dr. Heinecke also did not have to address the inconsistency in how Defendants approach statins: that statins could be, and were, given *with Lovaza* to severely hypertriglyceridemic patients to counteract Lovaza’s rise in LDL-C (*see, e.g.,* Trial Tr. 809:21–810:2 (Heinecke Direct)), yet purportedly could be given *without Lovaza* to simultaneously reduce both TGs and LDL-C in those very same patients. PPF ¶ 795. Were this true, there would have been no need to develop Lovaza, and the drug would not have been prescribed.

**B. Defendants Have Not Shown That a POSA Would Have Been Motivated to Arrive at the Claimed Invention**

Defendants also failed to prove that a POSA would have been led to eliminate DHA from Lovaza so as to arrive at an EPA-only treatment for severe hypertriglyceridemia. PPF ¶¶ 668–703. Setting aside that the prior art suggested that EPA would raise LDL-C, it also taught that DHA was, if anything, *cardioprotective*, offering advantages over EPA in terms of HDL-C, LDL particle size, blood pressure, heart rate, endothelial function, and fasting glucose. PPF ¶¶ 553–63, 673–85, 692. As the prior art taught that DHA had advantages over EPA, but EPA had none over DHA, the POSA would not have wanted to eliminate DHA from Lovaza. PPF ¶¶ 692, 695.

Defendants unsuccessfully attempt to disparage DHA. DPF ¶¶ 788–91. Their attacks on von Schacky’s preference for DHA, for example, are in vain (PPF ¶¶ 689–95), as are their arguments that DHA’s effects on HDL-C and LDL particle size touted by Mori were unimportant. PPF ¶¶ 556–61. And while Defendants contend that DHA’s advantages were irrelevant unless the art specifically *taught away* from using EPA (DPF ¶ 786), that is not the law. *See Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1069 (Fed. Cir. 2018) (“[E]ven if a reference is not found to teach away, its statements regarding preferences are relevant to . . . whether a skilled artisan would be motivated to combine that reference with another reference.”). The pertinent question is

1 whether Defendants have clearly and convincingly proven that a POSA would have been  
2 motivated to eliminate substantially all DHA from Lovaza. The answer is a resounding “no,” as  
3 the POSA would have understood that eliminating DHA would have only made Lovaza *worse*.  
4 PPF ¶ 695.

5 Defendants also rely on JELIS in an attempt to show motivation. DPF ¶ 790. But JELIS  
6 would not have led a POSA to eliminate DHA from Lovaza. JELIS did not study patients with  
7 severe hypertriglyceridemia, but instead patients with TG levels barely above normal. PPF ¶ 622.  
8 JELIS therefore taught nothing about the LDL-C effects of a TG-lowering agent in the severely  
9 hypertriglyceridemic, and offered no promise of avoiding LDL-C increases—or reducing  
10 cardiovascular risk—in such patients. PPF ¶¶ 622, 638, 770. JELIS also did not address in a  
11 sufficiently clear way administration of *substantially pure* EPA because the subjects in the study  
12 were also consuming substantial amounts of DHA. PPF ¶¶ 700–01. Indeed, WO ’118, which arose  
13 from JELIS, preferred combinations of DHA and EPA and taught that the Lovaza mixture could  
14 be used to achieve the benefits of JELIS. PPF ¶¶ 656–57. That JELIS would not have motivated a  
15 POSA to use high purity EPA in patients with severe hypertriglyceridemia was confirmed by Dr.  
16 Heinecke, who testified that, even after JELIS, “[y]ou’re not going to be using EPA to lower  
17 triglycerides above 500 in order to reduce cardiovascular risk. That’s not what any clinician would  
18 do.” PPF ¶ 702.

19 That DHA had desirable properties—and the POSA would therefore not have eliminated  
20 DHA wholesale from Lovaza—is confirmed by every cardiovascular outcome trial underway as  
21 of March 2008 (after JELIS): *all*, without exception, included substantial amounts of DHA. PPF  
22 ¶¶ 142–51. That these trials did not fail until later does not help Defendants: they are  
23 contemporaneous with the invention and clearly show what others—highly sophisticated  
24 companies and skilled principal investigators—thought was the best approach in using omega-3-  
25 fatty acids. Dr. Fisher confirmed this thinking when he recalled that neither he nor his colleagues  
26 believed that they “gotta get this DHA out of” Lovaza. PPF ¶ 696.

**C. Defendants Have Not Proven That It Would Have Been “Obvious to Try” the Claimed Invention**

As discussed above, a POSA would not have reasonably expected that *any* TG-lowering agent could avoid substantial increases in LDL-C in the severely hypertriglyceridemic. *See supra* at 14–16. This alone dooms any “obvious to try” argument. PPF ¶¶ 514–15 (Obvious to try requires “predictable solutions” that led to “anticipated success.”). Nor did Defendants show that there were a “finite number” of options that a POSA could pursue when seeking to lower TGs in the very high TG population without substantially increasing LDL-C. PPF ¶¶ 720–25. To the contrary, a POSA would have understood that there were “potentially infinite” options to pursue if seeking an improved treatment for severe hypertriglyceridemia that avoided LDL-C increases. PPF ¶ 721.

Defendants do not seriously dispute that “the universe of potential [options] [wa]s theoretically unlimited” (DPF ¶ 794), but argue that the Court should ignore most of those possibilities and focus on only those options that Defendants contend would have been obvious to try. But Defendants’ efforts to “funnel the formulator” to the “two options of EPA and DHA” are deeply flawed and steeped in impermissible hindsight. DPF ¶¶ 795–96.

Defendants suggest, for example, that a POSA could not have pursued a new type of fibrate or niacin formulation because drugs within those drug classes had previously produced LDL-C increases in the severely hypertriglyceridemic. DPF ¶ 795. But another omega-3-fatty acid formulation—Lovaza—had *also* failed to avoid such LDL-C increases. PPF ¶ 546. If prior failures with fibrates and niacin ruled out pursuing *any* type of new formulation within those classes, then the failure of Lovaza would also have ruled out pursuing anything within the omega-3-fatty acid class, including EPA. PPF ¶¶ 42, 715, 723, 837, 859. Defendants’ argument also overlooks other options that could have been pursued, such as any of a wide variety of possible fish oil compositions or a *combination* of existing agents. PPF ¶¶ 720–25. Indeed, Dr. Heinecke’s motivation theory—that one could improve compliance by taking a single pill instead of the two pills necessary when co-administering Lovaza with a statin—clearly pointed to a combination of Lovaza and a statin in a single pill or capsule. PPF ¶¶ 671, 876. And while Defendants contend

1 that the wide variety of EPA-DHA mixtures that were being studied in cardiovascular outcome  
2 trials as of 2008 should be ignored because their effects in the severely hypertriglyceridemic  
3 patient population had not been evaluated (DPF ¶ 801) neither had the effects of highly pure EPA.

4 The undeniable fact is that the prior art did not point to any particular avenue—whether  
5 niacin, fibrate, omega-3 fatty acid mixture or individual component (of which there are at least  
6 seven found in Lovaza), or entirely new agent—as most promising to reduce TGs in severely  
7 hypertriglyceridemic patients without raising LDL-C. This is the antithesis of obvious. *See, e.g.,*  
8 *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1356 (Fed. Cir. 2013) (reversing a finding of  
9 obviousness: “Where the prior art, at best gives only general guidance as to the particular form of  
10 the claimed invention or how to achieve it, relying on an obvious-to-try theory to support an  
11 obviousness finding is impermissible.”(citation omitted)).<sup>9</sup> Here, too, the invention was not  
12 obvious to try, as avoiding LDL-C increases in treatments for severe hypertriglyceridemia was  
13 decidedly not a promising field of experimentation—the perception was that TG-lowering would  
14 inherently increase LDL-C in severe hypertriglyceridemic patients—and there was no “general  
15 guidance” as to how to achieve a solution to that seemingly intractable problem. PPF ¶¶ 39–53.

16 That purified EPA was not obvious to try is further confirmed by the fact that no one had  
17 developed purified EPA for severe hypertriglyceridemia despite the product being available since  
18 the early 1990s. *See Leo Pharm.*, 726 F.3d at 1359 (“The intervening time between the prior art’s  
19 teaching of the components and the eventual preparation of a successful composition speaks  
20 volumes to the nonobviousness of the [challenged] patent.”). Defendants seek to avoid this  
21 conclusion by arguing that EPA had been tried. DPF ¶ 799. But Dr. Heinecke admitted that the  
22 LDL-C effects of EPA had never been studied in patients with severe hypertriglyceridemia as of  
23 the date of invention (PPF ¶ 508), and in any event, Defendants have conceded the novelty of the  
24 claimed methods. PPF ¶¶ 98, 497. The passage of time is particularly relevant here, as the LDL-C

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26  
27 <sup>9</sup> *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341 (Fed. Cir. 2009), upon which  
28 Defendants erroneously rely (DPF ¶ 657), is to the same effect, *see id.* at 1347.

1 increases seen in treating severely hypertriglyceridemic patients have been identified as a “major  
2 clinical concern” for decades. PPF ¶ 502.

3 Defendants now contend that it would have been “obvious to try” a *combination* of EPA  
4 *with a statin* for the seven claims that permit co-administration of a statin, and that this combination  
5 would have predictably avoided LDL-C increases. DPF ¶¶ 921–29. But this new argument is  
6 untenable. As Defendants themselves observe, the “obvious to try” doctrine is available only when,  
7 *inter alia*, “there is a design need or market pressure *to solve a problem*.” DPF ¶ 507 (citing *KSR*  
8 *Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) (emphasis added)). Defendants have made clear  
9 that the “problem” was having to co-administer a statin with the TG-lowering agent to address  
10 LDL-C increases in severe hypertriglyceridemia patients. PPF ¶ 728; DPF ¶ 815. The POSA would  
11 not have found it “obvious to try” an EPA-statin combination because that would not have been a  
12 solution to the problem of having to co-administer the TG-lowering agent with a statin. And if it  
13 was not a problem to co-administer a statin with a TG-lowering agent, then the predicate  
14 requirement for the “obvious to try” doctrine to apply—that there be “a design need or market  
15 pressure *to solve a problem*”—would not exist, and there would have been no motivation to modify  
16 Lovaza. Moreover, it was *not* predictable that EPA combined with a statin would avoid the rise in  
17 LDL-C in patients with *severe hypertriglyceridemia*. PPF ¶¶ 731–34; *see also Sanofi-Aventis*  
18 *Deutschland GmbH*, 748 F.3d at 1360 (“in the medical arts potential solutions are less likely to be  
19 genuinely predictable as compared with other arts such as the mechanical devices in *KSR*”)  
20 (internal quotation omitted). And, in any event, co-administration of EPA with a statin does not  
21 achieve the claimed invention, which requires administration of purified EPA to avoid increases  
22 in LDL-C caused by TG-lowering itself, not co-administration of another agent to address such a  
23 rise. Defendants’ new “obvious to try” theory involving co-administration of a statin is thus not  
24 viable.

#### 25 **D. Objective Indicia Reinforce the Non-Obviousness of the Asserted Claims**

26 Finally, Defendants cannot counter the compelling objective indicia underscoring the non-  
27 obviousness of the Asserted Claims. PPF ¶¶ 762–836.

1        *VASCEPA's LDL-C Neutrality.* Defendants dispute that there was a long-felt need for a  
 2 treatment that significantly lowered TGs in the severely hypertriglyceridemic without increasing  
 3 LDL-C. DPF ¶¶ 809–18. But LDL-C increases with TG-lowering agents had been of “major  
 4 clinical concern” since the 1970s (PPF ¶ 787), and Defendants acknowledge that Lovaza’s LDL-  
 5 C increases were “an important problem.” DPF ¶ 300. No previous treatment solved this  
 6 problem—including Epadel, which was not directed to patients with severe hypertriglyceridemia,  
 7 and had not been shown to avoid LDL-C increases in such patients. PPF ¶¶ 586–94, 793, 840. Nor  
 8 did the combination of statins and Lovaza, or statins alone, meet the long-felt need (had they done  
 9 so, there would have been no reason for the POSA to modify Lovaza). PPF ¶¶ 794–96.

10        Defendants also dispute that VASCEPA’s not raising LDL-C was unexpected. DPF  
 11 ¶¶ 819–22. But such increases are precisely what a POSA would have expected with EPA. PPF  
 12 ¶¶ 39–53, 764–65. And Defendants’ contention that the POSA would have expected to avoid large  
 13 LDL-C increases in patients with TG levels of exactly 500 mg/dL (DPF ¶ 820) is unsupported: the  
 14 Lovaza Statistical Review reported a large LDL-C increase across the *population* of severely  
 15 hypertriglyceridemic patients. PPF ¶ 662.

16        Defendants contend that there was no praise for VASCEPA avoiding LDL-C increases  
 17 (DPF ¶¶ 823–28), but VASCEPA was recognized, for example, as a “real advance in the treatment  
 18 of elevated triglycerides . . . all the benefit without the downside” and as showing that “[t]here’s  
 19 still room for small companies to do innovative things in this field.” PPF ¶ 816 & n.26. Contrary  
 20 to Defendants’ arguments, articles by Castaldo (PX 866) and Fialkow (PX 852) reflect further  
 21 praise beyond “repeating information from the product label” (DPF ¶ 826), and recognize  
 22 VASCEPA’s LDL-C neutrality as an “important difference” from “other add-on therapy options,”  
 23 which provides a clinical advantage by obviating the need for “periodic monitoring” of LDL-C.  
 24 PPF ¶¶ 813–14. The initial caveats of a few doctors about the top-line results of the MARINE trial,  
 25 which were later shown to be inconsequential, do not negate any of this praise. PPF ¶ 816 & n.26.

26        *Apo B Reduction.* Defendants also challenge the Examiner’s finding that the reduction in  
 27 apo B was unexpected (DPF ¶¶ 891–94), but the fact that VASCEPA reduced apo B in severely  
 28

1 hypertriglyceridemic patients, when the closest prior art, Lovaza, did not, was unexpected. PPF  
2 ¶¶ 766–67. Defendants’ reliance on Kurabayashi, Grimsgaard, and Nozaki in challenging this  
3 unexpected result (DPF ¶¶ 891–94) is flawed because, among other reasons, those studies involved  
4 patients with normal or barely elevated TG levels, which a POSA would not have looked to in  
5 forming an expectation. PPF ¶¶ 767, 871–72.

6 *REDUCE-IT*. Defendants’ challenges to the REDUCE-related objective indicia are  
7 meritless. Defendants dispute the *presumption* of nexus between the REDUCE-IT results and the  
8 Asserted Claims because multiple patents cover VASCEPA. DPF ¶¶ 833–34. But the Federal  
9 Circuit has long held that a presumption of nexus can apply where an invention is claimed by more  
10 than one patent. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1324–25 (Fed. Cir. 2016). Defendants  
11 suggest the Orange Book shows that the REDUCE-IT results are not related to severe  
12 hypertriglyceridemia (DPF ¶ 838), but that listing instead shows those results are relevant to *both*  
13 patients with severe hypertriglyceridemia and with mixed dyslipidemia. DPF ¶ 838.<sup>10</sup> Nor is a  
14 *presumption* of nexus necessary: carrying out the Asserted Claims—by administering 4 g/day of  
15 EPA to a severely hypertriglyceridemic patient—will provide the cardiovascular benefits observed  
16 in REDUCE-IT. PPF ¶¶ 776–85. Finally, Defendants are wrong that the REDUCE-IT results are  
17 not commensurate in scope with the Asserted Claims because they were “limited to patients with  
18

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19  
20 <sup>10</sup> Defendants wrongly suggest that patients with severe hypertriglyceridemia were excluded from  
21 the trial. DPF ¶¶ 850–52. While the exclusion criteria required patients to have TGs below 500  
22 mg/dL, patients with *controlled* severe hypertriglyceridemia were included—indeed, the  
23 cardiovascular disease history of the REDUCE-IT population shows that 148 patients had a history  
24 of TGs above 1000 mg/dL, indicating that even more had a history of TGs above 500. PX 1189  
25 (REDUCE-IT) at 128. Because the study criteria included a medication washout period prior to  
26 establishing the TG baseline, baseline TGs for the study expanded beyond the inclusion criteria (a  
27 point Defendants acknowledge (DPF ¶ 408)), and enrolled patients had baseline TG levels up to  
28 1400 mg/dL. PX 1189 (REDUCE-IT) at 195; Trial Tr. 1620:14–18 (Toth Direct). Thus, by design,  
the REDUCE-IT study included a significant number of severely hypertriglyceridemic patients,  
and it is thus unsurprising (and undisputed) that FDA approved VASCEPA for cardiovascular risk  
reduction in these patients (among others). PPF ¶ 165.

multiple cardiovascular risk factors that the claims do not require.” DPF ¶ 848. Most patients with TGs over 500 mg/dL have multiple risk factors for cardiovascular disease, with their elevated TGs one such risk factor, and other factors, like diabetes, often also present. PPF ¶ 28.

Defendants also dispute that VASCEPA met a long-felt need for a TG-lowering agent that reduces cardiovascular risk on top of statin therapy in the severely hypertriglyceridemic (DPF ¶ 854), but it is the first treatment for that population to achieve such risk reduction. PPF ¶ 798.<sup>11</sup> Defendants contend that JELIS already met this need (DPF ¶ 855), but JELIS studied patients with barely elevated TGs—not patients with very high TGs. PPF ¶¶ 799–806. In any event, because of JELIS’s many flaws, the medical community at large, including FDA and Dr. Fisher, did not accept its reported risk reduction at face value. PPF ¶¶ 621–42, 649–52, 658.

Defendants also contend that the REDUCE-IT results were not unexpected (DPF ¶ 872), but the widespread surprise at those results belies that contention. PPF ¶ 773. And in any event, the POSA certainly would not have expected that VASCEPA would reduce cardiovascular risk *in patients with severe hypertriglyceridemia* because the expected LDL-C increases would negate any cardiovascular benefits observed in patients with lower TG levels. PPF ¶ 770. Nor would it have been expected that VASCEPA would show a dramatic reduction in stroke or cardiovascular death, as JELIS did not report a significant benefit on either endpoint. PPF ¶¶ 771–72.

Defendants’ contention that these unexpected results are irrelevant because they are unrelated to the “goal of the inventive process” (DPF ¶ 878) is unavailing. Defendants cite no Federal Circuit case supporting this contention, nor *any* case remotely analogous to the facts here. The benefit of avoiding LDL-C increases when treating severely hypertriglyceridemic patients means that cardiovascular risk does not *worsen*. PPF ¶ 40. That VASCEPA not only avoids

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<sup>11</sup> Defendants are wrong that the new REDUCE-IT indication “is separate from Vascepa’s original indication for severe hypertriglyceridemia, which remains materially unchanged.” DPF ¶ 66. FDA significantly changed the severe hypertriglyceridemia indication—not just in the VASCEPA labeling, but also in Defendants’ labeling—by deleting the limitation of use stating that EPA’s effect on cardiovascular mortality and morbidity *in patients with severe hypertriglyceridemia* had not been determined. Trial Tr. 845:12–849:7 (Heinecke Cross); PPF ¶ 176.

1 increasing cardiovascular risk, but actually decreases it, is clearly related to the claimed invention  
2 and highly probative of non-obviousness. PPF ¶ 769.

3 Defendants also dispute skepticism (DPF ¶¶ 881–87), but there was widespread doubt  
4 about whether omega-3-fatty acids, including EPA, reduce cardiovascular risk. PPF ¶¶ 809–10.  
5 This was true before 2008, with one meta-analysis concluding that omega-3-fatty acids “do not  
6 have a clear effect on total mortality, combined cardiovascular events, or cancer.” PPF ¶ 141. That  
7 skepticism only grew after several additional outcome trials later failed. PPF ¶¶ 809–10. *Contra*  
8 Defendants (DPF ¶ 881), such post-invention skepticism, like other objective indicia arising after  
9 the invention, is relevant to non-obviousness. *Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367  
10 F.3d 1381, 1385 (Fed. Cir. 2004) (“Evidence developed after the patent grant is not excluded from  
11 consideration, for understanding of the full range of an invention is not always achieved at the time  
12 of filing the patent application.”). Nor is there merit to Defendants’ contention that expressions of  
13 surprise are not probative unless the speakers were previously aware of the prior art that formed  
14 the basis for the obviousness challenge. *See Eli Lilly & Co.*, 845 F.3d at 1374.

15 Finally, Defendants’ attempt to discount the widespread praise for REDUCE-IT on nexus  
16 grounds (DPF ¶ 888), and the contention that REDUCE-IT was merely “confirmatory” (DPF  
17 ¶ 890), are meritless, as there is a nexus between the Asserted Claims and REDUCE-IT, and  
18 REDUCE-IT broke new ground in the prevention of cardiovascular disease and treatment of severe  
19 hypertriglyceridemia. PPF ¶¶ 159–71, 775–85. The recent termination for futility of the  
20 STRENGTH trial of an EPA/DHA mixture—a trial whose anticipated success Defendants’ expert  
21 Dr. Fisher conceded was equally forecast by JELIS—provides compelling evidence of the  
22 unpredictability of clinical outcomes and the unreasonableness of Defendants’ assertion of  
23 expected success. Trial Tr. 1150:2–1151:25 (Fisher Cross).

24 *Commercial Success.* VASCEPA’s commercial success constitutes additional objective  
25 evidence of the non-obviousness of the Asserted Claims. PPF ¶¶ 818–31. Between 2013 and 2018,  
26 VASCEPA prescriptions grew from 174,000 to 1.3 million prescriptions (PPF ¶ 819), VASCEPA  
27 net sales grew from \$26 million to \$228 million (PPF ¶ 820), and its market share increased from  
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4% to 32% (PPF ¶ 821). Over its lifecycle, VASCEPA is expected to deliver a return exceeding the industry average by \$1.9 billion. PPF ¶¶ 822–24. VASCEPA’s commercial success is related to its patented features—namely VASCEPA’s avoidance of LDL-C increases—and not significantly due to promotion, marketing, pricing, or other factors, thus satisfying the nexus requirement. PPF ¶¶ 825–28. Moreover, all VASCEPA sales—including those to patients with TG levels below 500 mg/dL and increased sales due to the newly approved indication—have a nexus to the claimed invention. PPF ¶¶ 829–30.

#### IV. DEFENDANTS WAIVED THEIR WRITTEN DESCRIPTION DEFENSE

Defendants try to resurrect their § 112 defense for “lack of written description,” contending that it “was not waived” and that they should be able to pursue such a defense on appeal. DPF ¶¶ 958–61. Defendants are wrong. This Court previously held that Defendants’ failure to raise this defense in their opening reports prejudiced Amarin’s ability to respond with expert testimony, and that Defendants therefore “may not assert a written description defense at trial.” MSJ Opinion at 16–19, 24 (ECF No. 278). Defendants should not be permitted to assert their waived defense post-trial in order to argue its merits on appeal, after depriving Amarin of the opportunity to adduce responsive testimony during expert discovery and at trial.

DATED: February 28, 2020

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**CERTIFICATE OF SERVICE**

I hereby certify that I am an employee of McDonald Carano LLP and that on February 28, 2020, I electronically filed the foregoing **PLAINTIFFS' POST-TRIAL BRIEF** with the Clerk of the Court using the Court's CM/ECF system, which electronically served the attorneys of record set forth below.

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